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Gary Aston-Jones, Ph.D.

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Methods were developed for recording from locus coeruleus (LC) neurons in behaving monkeys using a microwire electrode holder allowing easy electrode repositioning in vivo. These techniques have vastly improved our data collection, so that we now routinely record from over 100 LC neurons per animal. Recordings of individual neurons are stable for periods of 30 min to 4 h. Methods were also developed for computer presentation of stimuli and task control in an oddball visual discrimination task. Other development included computer methods for data acquisition and analysis (on a separate machine) during this task.

Results indicated that most LC neurons are activated selectively for target stimuli during this task; they are not activated appreciably by nontarget stimuli. In addition, preliminary results suggest that tonic LC activity varies closely with the animal's attentiveness to the task. These results indicate that very small changes in the tonic discharge rate of LC neurons may produce marked changes in attentiveness, and that focused, attentive behavior may demand an intermediate level of LC discharge combined with robust phasic responses to meaningful sensory stimuli.

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LOCUS COERULEUS, VIGILANCE AND STRESS:
BRAIN MECHANISMS OF ADAPTIVE BEHAVIORAL RESPONSIVENESS

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ANNUAL TECHNICAL REPORT

The following is a list of publications during the period 12/15/89 to 12/14/90. Also included are selected publications after this time that were a direct result of work performed in this period that was supported in full or in part by AFOSR. These are included as there is usually a substantial delay for publications, and these publications reflect work perform.:d during the reporting period. Copies of each publication are attached.

Aston-Jones, G., Ennis, M., Shipley, M. and Williams, J.T. and Pieribone, V.A. Restricted afferent control of locus coeruleus revealed in anatomic, physiologic and pharmacologic studies. In: <u>The Pharmacology of Noradrenaline in the Central Nervous System</u>, C.A. Marsden and D.J. Heal, eds.,Oxford Univ. Press, 1990, pp: 187-247.

Astier, B., Van Bockstaele, E.J., Aston-Jones, G. and Pieribone, V.A., Anatomical evidence for multiple pathways leading from the rostral ventrolateral medulla (nucleus paragigantocellularis) to the locus coeruleus in the rat, <u>Neurosci. Lett.</u> 118: 141-146 (1990).

Aston-Jones, G. Drug-neuron interactions: The basis of neuropharmacology. <u>Contemp. Psychiat.</u> 9: 77-79 (1990).

Aston-Jones, G., Chiang, C. and Alexinsky, T., Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. <u>Prog. Brain Res.</u> 85: 501-520 (1991).

Aston-Jones, G., Valentino, R.J., Van Bockstaele, E. and Meyerson, A., Nucleus locus coeruleus and post-traumatic stress disorder: neurobiological and clinical parallels. In: <u>Catecholamine Function in Post-Traumatic Stress Disorder</u>, M. Murburg (ed), American Psychiatric Press, Wash., D.C. in press.

Aston-Jones, G., Rajkowski, J., Kubiak, P. and Akaoka, H., Acute morphine induces oscillatory discharge of noradrenergic locus coeruleus neurons in the waking monkey (submitted journal article).

Alexinsky, T. and Aston-Jones, G. Physiological correlates of adaptive behavior in the reversal of a light discrimination task in monkeys. Europ. J. Pharm. Suppl. 3: 149 (1990).

Alexi..ky, T., Aston-Jones, G., Rajkowski, J. and Revay, R.S. Physiological correlates of adaptive behavior in a visual discrimination task in monkeys. Soc. Neurosci. Abstr. 16: 164 (1990).

Clarke, C.D. and Aston-Jones, G. A general framework for developing theory in neuroscience. Soc. Neurosci. Abstr. 16: 1090 (1990).

Rajkowski, J., Akaoka, H., Kovelowski, C. J. and Aston-Jones, G. Decreased tonic discharge and induction of periodic bursting of locus coeruleus (LC) neurons after acute morphine in waking monkeys. Soc. Neurosci. Abstr. 17: 1541 (1991).

SUMMARY OF WORK SUPPORTED BY AFOSR
DURING THE PERIOD 12/15/89 TO 12/14/90.

I. Technical advances. A great deal of progress during the first year of our AFOSR award was in the form of important technical advances. These are summarized below under the subheadings (i) electrophysiological recording methods, and (ii) computerized experimental control and data collection and analysis.

A. Electrophysiological recording methods. We have implemented a technique previously developed by J. Rajkowski (co-PI) for recording neurons in deep structures of large brained mammals. Previously, Dr. Rajkowski showed that a simple head-mounted recording chamber with a guide cannula whose angle could be changed and which contained an inner cannula with the recording microwire electrodes could be used to record individual neurons in the striatum of cats. However, this technique had never been applied to smaller, deeper brainstem structures (e.g., nucleus locus coeruleus; LC) in primates. We found that these techniques also worked extremely well in the LC. We implanted one monkey with EEG electrodes and recording microdrives first in one hemisphere, then in the other, for recording single and multi-neuronal activity from the LC. Over the course of 8 months of experiments, we have recorded from over 200 LC neurons for periods ranging from 30 min to 4 h from this animal while he was performing an attentional task (described below). This was truly a phenomenal leap forward, as over the last 6 years of LC recordings from 8 monkeys using other techniques, we had recorded from a total of approximately 20 LC neurons stably over time. Besides allowing a much higher yield of stable LC units than previously possible, these new methods also allow very long-term recordings with low infection risk. In our animal recorded for more than 8 months and undergoing 2 separate surgeries for implantation of recording cylinders in each hemisphere, there was n o sign of infection or bone degeneration upon sacrifice. This is very unusual in chronic monkey recordings, and is mainly attributable to the novel recording cylinder design which is a closed system, never requiring exposure of the brain to the outside environment.

We also developed a method whereby we can obtain x-ray photographs of the recording electrode implants immediately after surgery, or at any subsequent time, with the animal's head in a stereotaxic plane. This allows rapid measurement of electrode placement relative to landmarks and stereotaxic coordinates. This method has also been an important factor in our ability to rapidly and reliably place microelectrodes into small, deep brain structures such as the LC.

B. Computerized experimental control and data collection and analysis. Our experimental design requires recording and storing several electrophysiological and behavioral signals simultaneously for later analysis. Previous experiments of this type required investigators to write their own software program from machine instruction routines onwards, often requiring 1 or more years before a productive computer software procedure was developed. Each such program developed was custom made for one particular application, so that it was difficult or impossible to use previously developed software for another (even similar) application. This situation has begun to change substantially, and we have taken advantage of a first generation of hardware and software that allows truly general purpose behavioral electrophysiology experimentation. We have implemented the Cambridge Electronic Design 1401 interface, with Spike 2, version 3, software, for our experiments. With this package and a 486/33 MHz microcomputer, we collect unit activity (of 2 cells simultaneously), EEG, eye movements (X and Y positions), pupil diameter, behavioral responses and stimulus presentations continuously onto a hard disk in real time. Our hard disk can hold approximately 15 h of recordings. We archive regularly onto a CD-ROM disk, which has 1 gigabyte capacity. The speed of this disk allows us to rapidly download archived files into the hard disk of a separate 486/33 MHz computer which is used only for data analysis. Here we use either routine provided by CED, or macro-level routines (of which we have written about a dozen), for rapid analysis of unit discharge in relation to sensory stimuli, behavioral responses, eye movements, pupillary diameter, or combinations of the above (e.g., unit activity for all bar releases within 500 msec after target stimuli). The implementation of this flexible and general purpose computer data acquisition and analysis package has proved crucial to allowing us to derive results from the large amount of complex data we collect in these experiments.

We have also developed a separate computer control system for flexible stimulus presentation and behavioral conditioning. Our system is loosely based on the Cortex program developed by Bob Desimone; Dr. Desimone has remained helpful in the continuing to improve this system.

II. Electrophysiological recordings from LC neurons.

Previous studies have implicated the nucleus LC in vigilance and adaptive responding to changing environmental stimuli. We examined this framework by recording neurons in the LC area of cynomolgus monkeys during performance of a "oddball" visual discrimination-vigilance task. Monkeys were trained with different colored lights as S+ or S-. A rapid lever release after the "oddball" S+ (10% of trials) was rewarded by juice. Hits and misses (for S+ stimuli),and false-alarms and correct non-responding (for S- stimuli) were recorded along with reaction times. Event-related potentials (ERPs) were also recorded from skull screws. Task parameters such as duration of the light, time to respond, interstimulus interval, S+/S- ratio, and duration of the sessions were systematically varied to alter task difficulty and attentiveness. Monkeys were also subjected to reversal training with this task..

Histologic reconstruction of all recording sites indicates that cells described here are noradrenergic LC neurons. Apart from cells that could not be driven by any aspect of the task (25%), many neurons could be classified as sensory (23%), motor (14%) or reward cells (2%). However, a large population of cells in the LC area (60 %) exhibited activity that was most closely related to the meaning of stimuli (i.e., driven by S+ but not S-). These cells altered their responsiveness to be activated by the new S+ stimuli during reversal training in close correlation with behavioral performance during acquisition of the new stimulus meaning. ERPs were also tightly coupled to S+ stimuli in this task and during stimulus reversal (correlation between ERP amplitudes and behavioral performance during reversal = 0.89). Thus, a strong relationship exists for activity of a population of cells in the LC area, cortical ERPs and adaptive behavior in a task of varying stimuli requiring sustained attention. In addition, a sizeable fraction of LC neurons (approx. 40%) are not activated by either S+ or S- stimuli, suggesting possibly the first example of physiologically defined heterogeneity within the LC.

More recent recordings from a second monkey have revealed similar properties of LC neurons. In addition, in preliminary studies we may have found a marked inverse correlation between tonic LC discharge rate and attentiveness, measured by the frequency of ocular fixation of a target spot, required to initiate behavioral trials. In the small number of cells analyzed, during waking there is a clear inverse correlation between the probability of ocular fixation (required to initiate a trial) and the tonic frequency of LC discharge. One possible interpretation is that high LC activity (above about 2- 4 Hz) is associated with an inability to focus attention for sustained periods (increased distractibility), while moderate LC activity (approx. 1-2 Hz) is conducive of focused attention and adaptive behavioral performance in a well-defined task. Lower levels of LC discharge (less than 0.5 Hz) are associated with drowsiness and poor task performance. These findings suggest that the most focused, attentive and adaptive behavior would occur with moderate levels of tonic LC discharge in combination with robust LC sensory responsiveness. Additional work in the next year will be directed at repeating these observations, and testing some of their most salient predictions.